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## Drug-Induced Hypersensitivity Syndrome With Hemophagocytic Lymphohistiocytosis Related to Piperacillin-Tazobactam: A Case Report

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Drug-induced hypersensitivity syndrome (DIHS), also known as drug response with eosinophilia and systemic symptoms (DRESS), is characterized by fever, rash, elevated eosinophils, internal organ impairment, and lymph node enlargement [1]. Hemophagocytic lymphohistiocytosis (HLH) is a rare, highly lethal disease that can be distinguished as primary or secondary HLH depending on whether the disease is caused by inherited or acquired abnormalities in immune regulation [2]. In recent years, several investigators have found that DIHS and HLH have similar clinical manifestations and laboratory findings, suggesting that both diseases cannot only coexist but may also have a common immune mechanism [3,4]. However, no cases of DIHS combined with HLH caused by piperacillin-tazobactam have been reported to date. We report the case of a patient confirmed as having DIHS combined with HLH related to piperacillin-tazobactam in our center. Informed consent was obtained from the patient and his family for the writing and publication of this article.

A 43-year-old man was admitted to hospital in January 2022 because of right chest pain with shortness of breath after activity for more than half a month. He had no previous underlying disease. Chest CT showed right pleural effusion with right lower lung atelectasis (Supplementary Figure 1A), and the patient was treated empirically with piperacillin-tazobactam combined with levofloxacin after admission. Levofloxacin was discontinued on day 3, as relevant tests showed no basis for atypical pathogenic infections. On day 12, the patient began to develop intermittent fever, and his temperature gradually increased to a maximum of 40.1°C on day 15 (Supplementary Figure 2). This was accompanied by a red rash distributed mainly over the trunk (Figure, A).



**Figure.** Rash on the right upper limb (A) and hematoma at the femoral artery puncture (B).

A follow-up chest CT revealed no progression of intrapulmonary lesions (Supplementary Figure 1B), and next-generation sequencing of the bronchial lavage fluid revealed *Streptococcus pneumoniae* and *Streptococcus pseudopneumoniae*. Given the suspicion of a delayed allergic reaction to piperacillin-tazobactam, the drug was discontinued and replaced with imipenem combined with linezolid. The patient later developed coagulation abnormalities, with markedly prolonged thrombin time (up to 160 seconds), accompanied by a decrease in fibrinogen and marked bleeding. A large hematoma appeared after blood collection from the right femoral artery (Figure, B), along with elevated liver enzymes and blood creatinine. Imipenem and linezolid were stopped on day 17. The patient's eosinophil count gradually increased to  $2.10 \times 10^9/L$ , and the leukocyte count increased to  $25.01 \times 10^9/L$  (Supplementary Figure 2). In addition, we found triglycerides to be significantly elevated (3.81 mmol/L).

Given the patient's clinical manifestations and laboratory findings, we suspected DIHS, with a RegiSCAR score of 7 (Supplementary Table 1) [5]. In addition, the severe coagulation disorders and significantly elevated triglycerides led us to perform further tests such as bone marrow aspiration biopsy and determination of sCD25, and NK-cell activity. The results showed that the patient's ferritin was as high as 3260 mg/mL, and the bone marrow aspiration results suggested phagocytosis with reduced NK cell activity. All these results supported a diagnosis of HLH according to the HLH 2004 diagnostic criteria (Supplementary Table 2) [6]. We then administered intravenous human immunoglobulin (pH 4, 20 g/d for 5 days), systemic corticosteroid therapy (intravenous methylprednisolone sodium succinate 1 mg/kg/d for 7 days, followed by slow tapering), and rational plasma transfusion according to the patient's coagulation results. On day 24, the patient's fever remitted, the generalized rash slowly subsided, and the relevant indices gradually returned to normal. One month after discharge, the patient's laboratory parameters had returned to normal, and the pulmonary lesions were gradually absorbed. To further clarify the allergenic drugs, we performed a drug lymphocyte stimulation test with piperacillin-tazobactam and levofloxacin 9 months after the patient was discharged from hospital. The results showed

marked lymphocyte proliferation by piperacillin-tazobactam (stimulation index [SI], was 628%), while the result for levofloxacin was negative (SI, 116%).

In addition to skin rash and fever, the patient experienced severe hepatic impairment, with transaminase levels more than 3 times the upper limit of normal, as well as renal impairment. This multisystem impairment caused by DIHS must also be taken into account when differentiating DIHS from common drug allergies. Coagulation abnormality was the most severe manifestation in the patient we describe, who had a significant tendency to bleed. The results for ferritin, triglycerides, bone marrow aspiration, and biopsy enabled us to confirm the diagnosis of HLH.

DIHS presents with elevated CD4/CD8 T-cell values, and untreated cases may eventually lead to increased proliferation and activity of macrophages, since inflammatory cytokines remain elevated. This may be one of the mechanisms by which HLH occurs in patients with DIHS [7]. Rosemary et al [8] reported a case with rash, fever, eosinophilia, and liver function impairment after 3 weeks of minocycline, which was clearly diagnosed as DIHS according to the RegiSCAR criteria. However, the patient had both splenomegaly and elevated ferritin and developed hypertriglyceridemia after initiation of corticosteroids, thus fulfilling 4 diagnostic criteria for HLH. Fortunately, the decrease in ferritin soon after initiation of corticosteroids led the researchers to quickly rule out HLH, as this condition often requires immunosuppressants and biological agents before symptoms and indicators improve.

Ammar et al [9] reported the case of a 45-year-old man diagnosed with DIHS after administration of sulfasalazine. The patient experienced concomitant reactivation of HHV-6 and HLH and eventually died owing to gastrointestinal bleeding. Yang et al [10] retrospectively analyzed the case data of 23 patients with DIHS with HLH and found that mortality was significantly higher than that of patients diagnosed with DIHS alone, reaching 24%. In addition, a large proportion of DIHS patients did not have a differential diagnosis of HLH, resulting in a missed diagnosis in most cases.

Therefore, it is recommended that screening for HLH (such as coagulation function, triglycerides, ferritin, spleen ultrasound) be routinely performed in patients with DIHS to ensure early diagnosis, early treatment, and reduced morbidity and mortality. To our knowledge, this is the first reported case of DIHS with HLH caused by piperacillin-tazobactam.

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#### Conflicts of Interest

The authors declare that they have no conflicts of interest.

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